Chapter 16
Micronutrient Deficiencies: Impact on Therapeutic Outcomes

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For health and well-being, humans must consume adequate quantities of key essential nutrients, such as protein, carbohydrates, fats, vitamins, and minerals to meet the biological requirements of the body. Many of these nutrients are considered essential since these cannot be manufactured within the body and are reliant upon dietary intake to meet requirements. At a basic level, malnutrition arises from decreased nutrient intake, or as a result of nutrient imbalances, i.e., a failure to meet nutrient requirements, an increase in nutrient losses, and/or alterations in nutrient utilization [1]. Malnutrition (undernutrition) in children has been recently defined as "an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes" [1]. Stunting or achieving the height that is "less than 2 standard deviations of the median age height in the reference population" [2] may be used as a broad indicator of inadequate dietary intake and malnutrition [3].

Malnutrition is directly or indirectly responsible for 45 % of global deaths among children who are under 5 years of age [4]. Malnutrition is classified as acute or chronic in nature. Acute malnutrition may arise from starvation, sometimes associated with humanitarian crises, sudden catastrophes, or seasonal food shortages [5]. *Severe* acute malnutrition, defined by a very low weight for height, by visible severe wasting, or by the presence of nutritional oedema, affects approximately 20 million children, mostly living in south Asia and sub-Saharan Africa [6].

Severe and/or acute malnutrition is also referred to as protein-calorie malnutrition (PCM), which is a result of low ingestion of protein and calories. Protein is an essential nutrient that has both structural and functional roles in the body. PCM has been identified as a contributor to higher mortality rates in infectious disease resulting from the negative impact on the immune system [7]. Some of the immunologi-

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cal changes that have been identified include altered immune cell populations, decreased natural killer cell activity, and decreases in immunoglobulin A as examples [7, 8].

Stemming from an interplay of socioeconomic disparity [9], poverty, chronic food insecurity, poor feeding practices, and illness [5], more than two billion individuals worldwide are chronically malnourished and suffer from micronutrient deficiencies. Chronic malnutrition may be more subtle in its manifestations, but can nonetheless have major health implications for populations. In early childhood, chronic malnutrition as a result of micronutrient deficiencies can lead to significant morbidity, given the impact on motor and mental development [10–13]. Micronutrient deficiencies which have an increased prevalence in children of developing countries are Vitamin A, zinc, and iron. A deficiency in one or several of these essential nutrients has been demonstrated to have an impact on the growth, development and immune status of children, and increase the susceptibility to several diseases [14].

Deficiencies arise in micronutrients for a variety of reasons. In developing countries, food choices are limited due to overwhelming poverty and poor agricultural yield. There is a reliance upon carbohydrate rich foods, such as rice or maize, as dietary staples, which are inherently poor sources of these essential nutrients [15]. A lack of adequate access to protein sources, such as meats, eggs, and dairy products, compounds the problem since reduced protein intake can also lead to a concomitant reduction in vitamin A, zinc, and iron [8, 16]. Illness can further exacerbate the malnourished state since dietary intake is reduced. Fever will necessitate an increase in catabolic processes and, in the case of diarrhea, increases the excretion of zinc. All of these factors can result in the vicious cycle of further depletion of essential nutrients from which the child may not be able to recover [14]. In the following sections, we will describe the role of these essential nutrients in health and illness.

Vitamin A

Vitamin A is a lipid soluble vitamin that is derived from preformed retinoids and provitamin carotenoids. Retinoids, such as retinoic acid and retinol, are available from animal sources such as liver, eggs, and dairy products, while leafy green or yellow vegetables and carrots are a source of the provitamin carotenoids of which beta-carotene has the greatest Vitamin A activity [17, 18]. Beta-carotene's bioavailability from plants sources ranges from 7 to 65 % and is converted to Vitamin A in the intestinal mucosa upon absorption [18]. The various forms of Vitamin A, retinoic acid and retinol, have roles in many areas of the body. Retinol is integral to the function and health of the eyes by acting in the differentiation of the corneal and conjunctival membranes and as an essential component of the rods of the retina [19]. Vitamin A regulates gene expression of structural proteins, enzymes, extracellular matrix proteins, and retinol binding proteins and receptors. Its involvement in cellular

differentiation and proliferation also impacts not only the integrity of the epithelium but also immune function [19]. Adequate levels of circulating natural killer cells, which have both antiviral and anti-tumor activity, require adequate levels of retinoic acid. Maturation and activation of B lymphocytes and production of inflammatory cytokines which stimulate T and B cell production require adequate levels of retinoic acid [19, 20]. Vitamin A improves iron absorption and metabolism [21].

A deficiency in Vitamin A can negatively impact both immune system function and the integrity of the epithelial barriers increasing susceptibility to infection. Vitamin A deficiency can also cause blindness. In accordance with WHO standards the prevalence of vitamin A deficiency has been measured indirectly by assessing the prevalence of night blindness (xerophthalmia) and a serum retinol concentration of <0.70 μmol/l. Night blindness has been found to affect 5.2 million preschool-age children (CI95%: 2.0–8.4 million); serum retinol concentration <0.70 μmol/l affect an estimated 190 million preschool-age children (CI95%: 178–202 million). In total, Vitamin A deficiency is determined to affect one-third of preschool-age children globally with Africa and South-East Asia being the most affected [22].

Zinc

Zinc is an essential mineral and has three distinct roles in the body: structural, catalytic, and regulatory [17]. Zinc is involved in catalyzing over 100 different enzymatic reactions and, structurally, in the correct folding of proteins [17]. Finally, zinc is involved in regulating gene expression through the activation of gene transcription, is involved in apoptosis, regulating normal synaptic processes, and cell-mediated immune function [17, 20]. In sum, zinc is key in physical growth and development, the functioning of the immune system, reproductive health, and neurobehavioral development [20]. The food sources of zinc are broad and include meat, beans, grains, and nuts; however, the bioavailability of zinc is highest in animal sources, since it is bound to protein. In grain sources, zinc is bound to phytates which inhibit its absorption [23]. A deficiency of zinc has been demonstrated to negatively affect the immune system through the decreased activity of both natural killer and T-cytolytic cells and a reduction in both the secretion and function of cytokines [24].

Based on demographic data, physiological requirements, and absorbable zinc content in national food supplies, it is estimated that approximately 15–20 % of the world's population is at risk of inadequate zinc intake [25]. In particular, the regions of sub-Saharan Africa and South Asia may be most affected. Moreover, it is estimated that the prevalence of zinc deficiency is higher in children less than 5 years of age than in the general population, owing to high nutrient density needs and rates of infection [25]. It is suggested that the prevalence of stunting among young children may be an indirect indicator of inadequate zinc intake, as zinc supplementation has been shown to increase both linear growth and weight gain in children [25, 26].

Iron

Iron is an essential mineral and has roles not only in the hemopoietic system but is also required for cell proliferation and oxidative metabolism [17, 20, 21]. Iron is available from both animal and plant sources, with animal source providing the more absorbable form of heme-iron. As with zinc, plant sources of iron are bound either to phytates or oxalic acid which inhibit its absorption [23]. Iron deficiency has been associated with reduced immune function, negatively impacting T-cell response, phagocytic activity, and immunoglobulin levels [8, 27, 28]. In addition, iron deficiency has been associated with reduced Vitamin A and carotenoid absorption [21].

In children, iron deficiency may arise from an inadequate diet, poor iron absorption, enhanced iron requirements during growth, and chronic blood loss resulting from parasites like hookworm. Young children have very high dietary iron requirements due to the rapid growth and expansion of red blood cell mass [29]. Iron deficiency can have major health implications, including impaired physical and cognitive development, increased risk of morbidity in children, and also accounts for approximately 20 % of maternal deaths [30]. Anemia affects 293 million children globally and is used as a surrogate indicator of iron deficiency. Almost half of all pre-school children (age 0–5) are affected by anemia; the highest prevalence of anemia is in Africa (68 %) and South-East Asia (66 %) followed by the Eastern Mediterranean (46 %) [31]. Country-specific information on the prevalence of anemia can be accessed by referring to the WHO's Vitamin and Mineral Nutrition Information System database [32]. Serum ferritin concentrations have also been measured for assessment of iron status and are the preferred method for determining the prevalence of iron deficiency in a population [33].

Iodine

Iodine is a mineral found in seafood, kelp, dairy products, and in plants which are grown in iodine-rich soil. The most common dietary source, however, is iodinated salt. Although it is estimated that 71 % of the world's population use iodized salt [34], iodine intake of 285 million school-age children worldwide is still deemed insufficient, as defined by urinary iodine concentrations below 100 μg/L [35]. The largest number of children affected is in South-East Asia, Africa, and the West Pacific. The highest proportions of iodine insufficiency, albeit mild, are found in Europe (59.9 %) and South-East Asia (39.9 %) [35]. Deficiencies in iodine are associated with a wide range of physical and cognitive deficits in children [36] and are the greatest cause of preventable brain damage in childhood [37]. It has been shown that people living in areas affected by severe iodine deficiency may have an intelligence quotient (IQ) of up to 13.5 points below that of those from comparable communities in areas where there is no iodine deficiency [38]. Moreover, a range

of iodine deficiency disorders, related to hypothyroidism resulting from insufficient iodine intake, can plague the growth and productivity of whole communities who are not receiving enough iodine as part of their diets [38]. While significant progress has been made due to salt iodination, moderate to severe iodine deficiency was still reported in 14 countries in 2004 [37]. The WHO has mapped population iodine status in school-aged children over a 5-year period by measuring iodine excretion in urine. The prevalence of iodine deficiency, based on goiter prevalence and/or urinary iodine, in over 150 countries worldwide can be accessed through WHO [32].

Addressing Key Nutrient Deficiencies and the Resulting Impact on Therapeutic Outcomes

Globally, the leading causes of death in children less than 5 years of age are pneumonia, preterm birth complications, birth asphyxia, diarrhea, and malaria [39]. It is also recognized that both maternal and child malnutrition are exacerbating factors in about half of these childhood fatalities. In children with diarrhea, measles, and malaria, vitamin A deficiency increases the risk of mortality by 20–24 %, while a zinc deficiency increases this risk by 13–21 % [10, 12, 40]. These nutrient deficiencies are believed to not only compromise child health but can also reduce a country's economic advancement by 8 % [13].

A variety of different strategies have been undertaken to improve the nutritional status of children in low and middle-income countries. In 2010, a framework entitled, Scaling Up Nutrition (SUN) was developed to deliver 13 different nutrient interventions in 36 different countries aimed at reducing undernutrition targeting children under 2 years of age, however; the program also provided benefits to children up to the age of 5 years and included interventions targeting maternal nutrition [41]. The interventions identified in the framework leveraged supplementation strategies for Vitamin A and zinc, iron fortification of staple foods, and multiple nutrient powders [41, 42]. Since its inception, the number of countries participating in the program has grown to 46 [43].

The WHO has created a central database which consolidates the nutrition initiatives undertaken by countries and various groups worldwide. The Global database on the Implementation of Nutrition Action (GINA) accepts data from many different organizations such as Flour Fortification Initiative, Mapping Actions for Food Security & Nutrition, FAOLEX, SUN movement, IBFAN World Breastfeeding Trends Initiative, Micronutrient Initiative, Global Alliance for Improved Nutrition, Iodized salt consumption, Vitamin A supplementation coverage, Coverage Monitoring Network, World Vision International, and 1,000 days [44]. The scope of the database is much broader and goes beyond the supplementation and fortification programs to help children under the age of 5 years, and is designed as an interactive platform for sharing nutrition policies and actions.

Vitamin A

Mayo-Wilson et al. conducted a meta-analysis of randomized controlled trials on Vitamin A supplementation versus either placebo or no treatment and the impact on all-cause mortality and cause specific mortality in children under 5 years of age. The dosing strategies were variable in the studies, both dose and duration. The meta-analysis showed that Vitamin A supplementation was associated with a 24 % reduction in all-cause mortality (risk ratio: 0.76, CI95%: 0.69–0.83), with moderate heterogeneity [45]. Additionally, there was a 27 % reduction (risk ratio: 0.72, CI95%: 0.57–0.91) in mortality from diarrhea; with respect to measles, there was a non-significant reduction in mortality (risk ratio: 0.80, CI95%: 0.51–1.24) but a significant reduction in the incidence of measles (risk ratio: 0.50, CI95%: 0.37–0.67) [45]. The result of the cumulative meta-analysis demonstrates that Vitamin A supplementation contributes to the reduction of mortality in children under 5 years; however, the most appropriate dosing strategy to maximize this benefit requires further investigation [45].

A meta-analysis on the impact of 100,000 or 200,000 international units (IU) of Vitamin A administered quarterly to HIV infected children between 1 and 5 years of age ($n=267$) found a 45 % reduction in all-cause mortality (risk ratio: 0.55, CI95 % 0.37–0.82) [46]. The supplementation and follow-up period ranged between 17 and 24 months in these studies. A positive impact on reducing the persistence of the cough associated with pneumonia [47], diarrhea [48], and AIDS-related deaths [49] were also reported.

In the case of sickle cell disease (see Chap. 27), there is some evidence that children affected may have lower micronutrient levels [50]. Despite similar dietary intake, children with SCD had lower red blood cell zinc levels, lower serum vitamin A levels, and lower urine nitrogen levels versus controls [50]. However, a 12-month vitamin A supplementation program in US children with SCD did not improve serum retinal values in a randomized, double-blind, placebo controlled trial, suggesting that (1) further research is needed and (2) higher doses than the recommended dietary allowance of vitamin A may be required to achieve adequate Vitamin A status [51].

Zinc

Yakoob et al. completed a meta-analysis of zinc supplementation randomized controlled trials in children less than 5 years of age to determine the impact on diarrhea, pneumonia, and malaria [52]. The median dose of zinc reported in the meta-analysis was 10 mg/day for at least 6 months. The results suggest a non-significant decrease in all-cause mortality (risk ratio: 0.95, CI95%: 0.88–1.02), and mortality from diarrhea (risk ratio: 0.91, CI95%: 0.76–1.09) with zinc supplementation at this level. There was a significant reduction in the mortality from pneumonia (risk ratio: 0.80,

CI95%: 0.67–0.96) and in the incidence of both diarrhea (risk ratio: 0.87, CI95%: 0.81–0.94) and pneumonia (risk ratio: 0.81, CI95%: 0.73–0.90). A subsequent study that was published after the meta-analysis completely investigated the impact of zinc supplementation at a dose of 20 mg of zinc gluconate daily for 7 days ($n = 127$) versus placebo ($n = 129$), as an adjunct therapy to standard treatment in children admitted with pneumonia in Uganda. The findings suggest that there was no impact on clinical recovery; however a non-significant reduction in the number of fatalities was reported in the zinc supplemented group (risk ratio: 0.7, CI95%: 0.2–2.2) [53].

Studies of zinc supplementation in both acute and chronic diarrhea in children under 5 years of age have been completed. Lazzerini et al. found that zinc supplementation of 5 mg/day significantly reduced the duration of acute diarrhea in children between the age of 6 months and 5 years at all time points evaluated (Days 3, 5, and 7) [54].

The impact of zinc supplementation in children with SCD has been systematically reviewed. In SCD, there is an increase in urinary zinc excretion that, in combination with inadequate dietary intake, can contribute to zinc deficiency [55]. Dekker et al. concluded that zinc supplementation could possibly reduce the incidence of infection and vaso-occlusive crises when zinc was given for at least 1 year [56]. However, further research is required to determine whether zinc supplementation could have an impact on reducing mortality in children with SCD.

In HIV+ children, the impact of zinc supplementation appears limited. One study investigated the effect of 10 mg of zinc sulfate for 6 months. There were no negative effects found; no increase in viral load occurred and there was a reduction in the incidence of diarrhea in the children receiving supplementation [46, 57]. A subsequent study investigated the impact of zinc supplementation at a dose of 20 mg of zinc gluconate daily for 7 days ($n = 27$) versus placebo ($n = 28$), as an adjunct therapy to standard treatment for those HIV infected children admitted with pneumonia in Uganda. There was a reduction in the number of fatalities in the zinc supplemented group (risk ratio: 0.1, CI95%: 0.0, 1.0); however, zinc supplementation had no impact on clinical recovery times [53].

Iron

The impact of iron supplementation programs on nutrition and development in children under 12 remains uncertain [58]. A 2009 Cochrane review on the impact of iron supplementation on mortality and morbidity outcomes in HIV infected children was inconclusive [59]. While there is evidence to support the reduction of anemia and iron deficiency with both daily and intermittent iron supplementation, in malaria endemic areas the supplementation of iron in children can result in an increase in the severity of the illness and perhaps death [60, 61]. The WHO recommends that malaria prevention and treatment programs be in place in malarial endemic areas prior to the administration of iron supplementation [62].

Multiple Nutrient Supplementation

A recent randomized controlled trial compared zinc supplementation or placebo with vitamin A, in 852 apparently healthy 2–5 year-old children in Indonesia, on the incidence and duration of upper respiratory tract infections (URTI) over 4 months [63]. Children in the study were randomized to receive either 10 mg of elemental zinc ($n=399$) or placebo ($n=399$) daily in syrup for four months. All children in the study receive 200,000 IU of vitamin A at month 2 after recruitment as part of a bi-annual national supplementation program. Findings from the study suggest that the combination of zinc and vitamin A reduced the duration of the URTI by 20 % ($p=0.01$), producing a greater reduction versus zinc supplementation alone (12 % reduction in duration ($p=0.09$)). The authors suggest that the interaction effects of these two nutrients could result from the impact that these nutrient have on improving epithelial integrity and immune response.

The impact on therapeutic outcomes from the use of multiple nutrient supplementation powders which combine several essential nutrients together in a format that can be mixed with prepared food in the home requires more investigations. Evidence suggests that this form of supplementation can improve both iron and vitamin A deficiency; however, there is also evidence to suggest that the use of multiple micronutrients formulation increases the incidence of diarrhea [61, 64].

Conclusions

Undernutrition contributes to 45 % of the global deaths of children under 5 years of age. Supplementation programs in developing countries for Vitamin A and zinc have been shown to reduce all-cause mortality, mortality from diarrhea in both HIV infected and uninfected children, and the incidence of measles in HIV negative children. Zinc, as an adjunct therapy to standard treatment for pneumonia, also reduced the mortality rate in both HIV infected and uninfected children. There are gaps in our understanding of the most appropriate dosing strategies for Vitamin A to maximize the benefits associated with supplementation. What, if any, synergies may result from multiple nutrient supplementation or fortification strategies require further investigation.

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